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A FACILE PREPARATION OF 1,2,3-TRIAROYLINDOLIZINES

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ABSTRACT: Fourteen 1,2,3-triaroylindolizines were prepared conveniently by oxidation of corresponding N-aracyl pyridinium or substituted pyridinium bromides with a versatile oxidant TPCD [$(Py_4Co(HCrO_4)_2$, tetrakis-pyridino-cobalt (II) dichromate] in 12-42 % yields.

In our previous work, we have described the structure of oxidant TPCD, which is a bi-metal complex with pyridine prepared easily by adding pyridine to the aqueous solution of chromium trioxide and cobalt (II) acetate, and its some properties in the oxidation of organic compounds.[1,2,3] Benzylic halides, for example, can be oxidized by TPCD in DMF to corresponding carbonyl compounds in moderate to high yields. Under the same condition, 2-bromopropiophenone was oxidized to 1-phenyl-1,2-propandione in 40% yield. However, a yellow crystalline compound with high melting point was obtained instead of the expected phenylglyoxal when α-bromoacetophenone was treated with TPCD. The data of IR, ^{1}H NMR, MS spectra and the results of elemental analyses of this compound all

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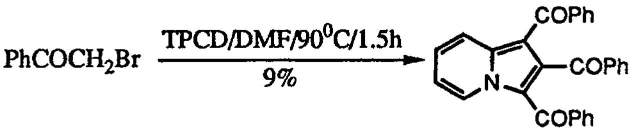


(1)

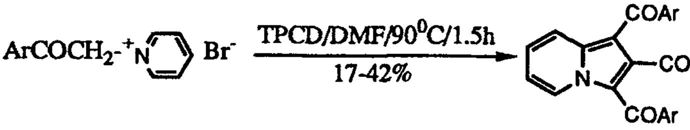
2a

were in agreement with those of 1,2,3-tribenzoylindolizine (**2a**). It is obvious that the pyridine ring in 1,2,3-tribenzoylindolizine (**2a**) comes from the oxidant TPCD (scheme 1).

A number of publications have reported syntheses and synthetic mechanisms for indolizines.[4-8] Taylor et al [9] obtained 1,2,3-tribenzoylindolizine (**2a**) in 37% yield by reaction of N-phenacypyridium bromide (**1a**) with iodine overnight at room temperature and then at 100 °C for 4 h. Schutze and Krohnke[10] treated **1a** first with 2 equivalents of phenylglyoxal to get 1,2,3-tribenzoyl-d-1,8-dihydroindolizine and then oxidized the latter with air in piperidine-ethanol solution or dehydrogenated on Pd/C to give **2a** in about 40% yield. When we tried to use **1a** as a source of pyridine and oxidized **1a** with TPCD, a better yield of **2a** was obtained. Other 1,2,3-triaroylindolizines **2b**-**2n** were prepared by the same method. The reaction presents a very easy and useful method to synthesize 1,2,3-triaracylindolizines from N-aracyl pyridinium or substituted pyridinium bromides alone. Comparing with ref. 9 and ref. 10 mentioned above, this reaction is run under milder conditions, having shorter times and cheaper reagents (scheme 2).

Compounds **2k**, **2l** were obtained by oxidation of N-phenacyl imium salts (**1k**, **1l**) prepared respectively from methyl isonicotinate and isoquinoline. The oxidation of N-phenacyl methyl nicotinate bromide (**1m**) gave two isomers **2m** and **2n**.

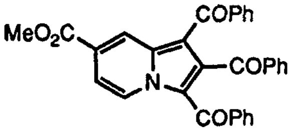
We hypothesize that a part of N-phenacypyridium bromide (**1a**) is oxidized to phenylglyoxal at first, then condenses with the imium salt catalyzed by pyridine, and then oxidized to 1,2,3-triaracylindolizines. We think that the reaction could proceed according to a 1,5-dipolar cycloaddition mechanism even though we have



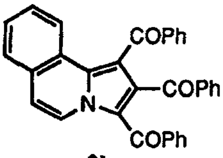
(2)

1a-j **2a-j**

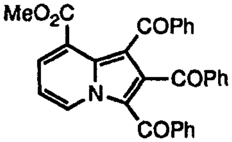
1,2	Ar	1,2	Ar
a.	C_6H_5	f.	$4\text{-}ClC_6H_4$
b.	$4\text{-}MeC_6H_4$	g.	$4\text{-}BrC_6H_4$
c.	$2,4\text{-}Me_2C_6H_3$	h.	$4\text{-}MeOC_6H_4$
d.	$3,4\text{-}Me_2C_6H_3$	i.	$4\text{-}NO_2C_6H_4$
e.	$4\text{-}PhC_6H_4$	j.	β-naphthyl



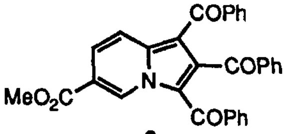
2k



2l



2m



2n

not enough evidence yet. However, the experimental results show that the components of TPCD are essential. The expected compounds **2a** could not have been produced by reactions of **1a** with its components cobalt (II) acetate or chromium trioxide alone under the same conditions respectively.

EXPERIMENT SECTION

All melting points are uncorrected and measured with a Yanaco MP-500 apparatus. IR spectra were recorded on a Nicolet FT-IR 5DX spectrometer with KBr pellets. ^{1}H NMR spectra were recorded on a JEOL JNM-PMX 60SI spectrometer at ambient temperature in $CDCl_3$ with TMS as an internal reference and mass spectra on a VG ZAB-HS spectrometer with 70 ev. Elemental analyses were performed on a Perkin-Elmer 240-C instrument.

Preparation of 1,2,3-triaroylindolizines 2a-2n; General Procedure: A solution of pyridine salt **1** (a-m, 10 mmol) and TPCD (4.0 g, 6.5 mmol) in DMF (40 mmol) was stirred at 90 ^{0}C for 1.5 h. The mixture was then cooled down to room temperature and poured into 5% aqueous solution of hydrochloric acid (100 mL). The solid was collected on a Buchner funnel and purified by vacuum chromatography (VLC) [silica gel, 10 μm, 2.5x5 cm, 20% ethyl acetate in petroleum ether (60-90 ^{0}C)]. After recrystallization of them from suitable solvents, pure compounds **2a-n** were obtained as yellow crystals which were idenfied with IR, ^{1}H NMR, MS and microanalyses.

2a, yield 32%. m.p. 223-5 ^{0}C (EtOH) (Lit.[9,10] m.p. 223-4 ^{0}C). Anal. Calcd. for $C_{29}H_{19}NO_3$: C, 81.10; H, 4.46; N, 3.26. Found: C, 81.13; H, 4.43; N, 3.58. IR: ν 3010, 1655, 1620, 1605, 1590, 1220, 760, 700 cm^{-1}. ^{1}H NMR: δ 7.00-7.60 (m, 17H, ArH), 8.13 (dd, J = 0.5 Hz, J = 8.5 Hz, 1H, ArH), 9.75 (dd, J = 0.5 Hz, J = 7.0 Hz, 1H, ArH) ppm. MS, *m/z* (%): 429 (M$^+$, 100), 352 (24.0), 274 (12.4), 105 (36.0), 77 (8.70).

2b, yield 36%. m.p. 203-5 ^{0}C (EtOH). Anal. Calcd. for $C_{32}H_{25}NO_3$: C, 81.51; H, 5.34; N,2.97. Found: C, 81.35; H, 5.31; N, 2.72. IR: ν 1655, 1600, 900, 700 cm^{-1}. ^{1}H NMR: δ 2.26 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 6.80-7.60 (m, 14H, ArH), 8.03 (d, J = 8.0 Hz, 1H, ArH), 9.62 (d, J = 7.0 Hz, 1H, ArH) ppm. MS, *m/z* (%): 471 (M$^+$, 100), 380 (24.9), 288 (28.2), 91 (39.0).

2c, yield 17%. m.p. 121-3 ^{0}C (EtOAc-Petroleum ether). Anal. calcd. for $C_{35}H_{31}NO_3$: C, 81.84; H, 6.08; N, 2.73. Found: C, 81.52; H, 6.10; N, 2.59. IR:

ν 2900, 1650, 1605, 778 cm^{-1}. ^{1}H NMR: δ 1.91 (s, 3H, CH_3), 2.09 (s, 6H, $2CH_3$), 2.13 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 6.50-7.65 (m, 11H, ArH), 8.07 (d, J = 8.8 Hz, 1H, ArH), 9.96 (d, J = 7.2 Hz, 1H, ArH) ppm. MS, *m/z* (%): 513 (M$^+$, 37.5), 380 (44.5), 274 (22.8), 133 (100), 105 (32.7).

2d, yield 22%. m.p. 155-7 ^{0}C (EtOH). Anal. calcd. for $C_{35}H_{31}NO_3$: C, 81.84; H, 6.08; N, 2.73. Found: C, 81.30; H, 6.30; N, 2.34. IR: ν 2900, 1650, 1605, 775 cm^{-1}. ^{1}H NMR: δ 1.92 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 6.80-7.60 (m, 11H, ArH), 8.20 (d, J = 8.5 Hz, 1H, ArH), 9.68 (d, J = 7.0 Hz, 1H, ArH) ppm. MS, *m/z* (%): 513 (M$^+$, 100), 408 (9.0), 133 (30.2), 79 (7.8).

2e, yield 25%. m.p. 180-2 ^{0}C (EtOAc-Petroleum ether). Anal. calcd. for $C_{47}H_{31}NO_3$: C, 85.82; H, 4.75; N, 2.13. Found: C, 85.78; H, 4.57; N, 2.01. IR: ν 3030, 1663, 1603, 1503, 746, 693 cm^{-1}. ^{1}H NMR: δ 7.25-7.70 (m, 29H, ArH), 8.10 (d, J = 8.0 Hz, 1H, ArH), 9.71 (d, J = 7.0 Hz, 1H, ArH) ppm. MS, *m/z* (%): 657 (M$^+$, 100), 504 (8.6), 350 (14.5), 181 (22.7), 152 (23.3).

2f, yield 34%. m.p. 183-5 ^{0}C (EtOH). Anal. calcd. for $C_{29}H_{16}Cl_3NO_3$: C, 65.37; H, 3.03; N, 2.63. Found: C, 65.27; H, 3.03; N, 3.00. IR: ν 3050, 1660, 1610, 1580, 850, 775, 670 cm^{-1}. ^{1}H NMR: δ 7.05-7.65 (m, 14H, ArH), 8.10 (d, J = 10.0 Hz, 1H, ArH), 9.80 (d, J = 7.5 Hz, 1H, ArH) ppm. MS, *m/z* (%): 533 (M$^+$, 63.0), 420 (22.2), 300 (28.1), 308 (20.1), 139 (100), 111 (54.7).

2g, yield 30%. m.p. 189-191 ^{0}C (EtOH-$CHCl_3$). Anal. calcd. for $C_{29}H_{16}Br_3NO_3$: C, 52.29; H, 2.42; N, 2.10. Found: C, 52.16; H, 2.42; N, 2.05. IR: ν 3050, 1665, 1612, 1580, 850, 775, 675 cm^{-1}. ^{1}H NMR: δ 7.05-7.70 (m, 14H, ArH), 8.08 (d, J = 8.0 Hz, 1H, ArH), 9.73 (d, J = 7.0 Hz, 1H, ArH) ppm. MS, *m/z* (%): 667 (M$^+$, 100), 510 (17.0), 352 (9.3), 274 (19.7), 183 (49.2).

2h, yield 33%. m.p. 157-9 ^{0}C (EtOH). Anal. calcd. for $C_{32}H_{25}NO_6$: C, 73.90; H, 4.85; N,2.70. Found: C, 73.60; H, 4.85; N, 2.41. IR: ν 2900, 2800, 1645, 1590, 845, 770 cm^{-1}. ^{1}H NMR: δ 3.67 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.52-7.80 (m, 14H, ArH), 8.06 (d, J = 8.0 Hz, 1H, ArH), 9.53 (d, J = 7.0 Hz, 1H, ArH) ppm. MS, *m/z* (%): 519 (M^+, 100), 412 (11.7), 304 (12.0), 135 (70.4), 82 (47.9).

2i, yield 34%. m.p. 283-5 °C (DMF), Anal. calcd. for $C_{29}H_{16}N_4O_9$: C, 61.71; H, 2.86; N, 9.93. Found: C, 61.89; H, 2.96; N, 9.89. IR: v 3035, 1670, 1610, 1595, 843, 705 cm^{-1}. ^1H NMR spectrum was not obtained due to small solubility in solvent. MS, *m/z* (%): 564 (M^+, 100), 519 (8.0), 424 (10.5), 149 (10.0), 94 (12.0).

2j, yield 23%. m.p. 138-140 °C (EtOAc-Petroleum ether). Anal. calcd. for $C_{41}H_{25}NO_3$: C, 84.96; H, 4.35; N, 2.42. Found: C, 84.72; H, 4.26; N, 2.28. IR: v 3030, 1650, 1615, 820, 755 cm^{-1}. ^1H NMR: δ 6.84-7.93 (m, 23H, ArH), 8.27 (d, J = 9.0 Hz, 1H, ArH), 9.83 (d, J = 7.5 Hz, 1H, ArH) ppm. MS, *m/z* (%): 579 (M^+, 100), 519 (14.3), 424 (35.7), 299 (37.9), 127 (95.8), 82 (58.9).

2k, yield 28%. m.p. 142-4 °C (EtOAc-Petroleum ether). Anal. calcd. for $C_{36}H_{21}NO_5$: C, 76.38; H, 4.34; N, 2.87. Found: C, 76.29; H, 4.30; N, 2.89. IR: υ 3020, 1715, 1650, 1620, 775, 715, 690 cm^{-1}. ^1H NMR: δ 3.98 (s, 3H, $COOCH_3$), 7.03-7.68 (m, 15H, ArH), 7.73 (dd, J = 2.0 Hz, J = 8.0 Hz, 1H, ArH), 8.83 (d, J = 2.0 Hz, 1H, ArH), 9.62 (d, J = 8.0 Hz, 1H, ArH) ppm. MS, *m/z* (%): 487 (M^+, 100), 410 (31.1), 382 (12.2), 332 (18.8), 105 (74.7), 77 (63.6).

2l, yield 42%. m.p. 218-220 °C (EtOAc-Petroleum ether). Anal. Calcd. for $C_{33}H_{21}NO_3$: C, 82.31; H, 4.60; N, 3.14. Found: C, 82.66; H, 4.41; N, 2.92. IR: v 3000, 1650, 1610, 955, 735, 689 cm^{-1}. ^1H NMR: δ 7.20-8.20 (m, 19H, ArH), 8.40 (dd, J = 2.0 Hz, J = 7.5 Hz, 1H, ArH), 9.43 (d, J = 8.0 Hz, 1H, ArH), ppm.MS, *m/z* (%): 479 (M^+, 100), 402 (32.2), 324 (16.1), 240 (6.6), 105 (67.6), 77 (52.0).

2m, yield 27%. m.p. 205-7 °C (EtOAc-Petroleum ether). Anal. calcd. for $C_{36}H_{21}NO_5$: C, 76.38; H, 4.34; N, 2.87. Found: C, 76.40; H, 4.09; N, 2.88. IR: v 3010, 1720, 1650, 1615, 735, 705, 685 cm^{-1}. ^1H NMR: δ 3.60 (s, 3H, $COOCH_3$), 7.10-7.77 (m, 15H, ArH), 7.82-8.14 (m, , 2H, ArH), 10.03 (dd, J = 1.0 Hz, J = 8.0 Hz, 1H, ArH) ppm. MS, *m/z* (%): 487 (M^+, 100), 410 (65.8), 378 (20.0), 105 (67.6), 77 (57.3).

2n, yield 19%. m.p. 214-6 °C (EtOAc-Petroleum ether). Anal. calcd. for $C_{36}H_{21}NO_5$: C, 76.38; H, 4.34; N, 2.87. Found: C, 76.25; H, 4.40; N, 2.90. IR: ν 1715, 1670, 1620, 765, 740, 715, 700 cm^{-1}. ^1H NMR: δ 4.01 (s, 3H, $COOCH_3$), 7.03-7.68 (m, 15H, ArH), 8.70 (m, 2H, ArH), 10.31 (d, J = 1.0 Hz, 1H, ArH) ppm. MS, *m/z* (%): 487 (M^+, 100), 410 (27.0), 382 (12.9), 332 (16.5), 105 (83.1), 77 (71.2).

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